REMARKS

Status Summary

Claims 1-4, 6-17, and 37-39 are pending and have been examined by the U.S. Patent and Trademark Office (hereinafter, "Patent Office"). Claims 1, 3, 10, 12, and 37 have been rejected under 35 U.S. C. § 102(b). Claims 1-4, 6-17 and 38-39 have been rejected under 35 U.S.C. §103(a).

Claims 1-4, 6-17, 37, and 39 have been canceled and new Claims 40-45 have been added by the present Amendment. Therefore, Claims 38, and 40-45 are currently pending. New Claims 40-45 comprise the subject matter of claims originally dependent from Claim 1 (i.e., claims 2, 3, 6, 7, 8 and 9), rewritten to depend either directly or indirectly from Claim 38. Therefore, support for new Claims 40-45 can be found throughout the specification and in the claims as originally filed. No new matter is introduced by new Claims 40-45.

Claim Rejection - 35 U.S.C. § 102

Claims 1, 3, 10, 12, and 37 stand rejected by the Patent Office under 35 U.S.C. § 102(b) as being anticipated by the journal article of Brown et al. (*Hypertension*, 1998; 32:965-971), hereinafter referred to as "Brown et al."; or Uehara et al. (*J. Cardiovasc Pharmacol Therapeut*, 1998: 3(4):327-36), hereinafter referred to as "Uehara et al.".

The Patent Office contends Brown et al. teaches the administration of an ACE inhibitor to healthy patients because Brown et al. teaches that not all test subjects

ingest a salt limited diet. Therefore, the Patent Office argues, subjects that did not ingest a salt limited diet did not have an activation of the renin-angiotensin system and as such these subjects fall within the definition of "healthy", as defined in the specification.

The Patent Office further contends Uehara et al. teaches the study of ACE inhibition on PAI-1 in diabetic rats, and that PAI-1 concentrations in plasma were significantly increased in untreated diabetic rats compared to control non-diabetic rats. Although the rejected claims state the treatment is for reducing the risk of cardiovascular disease, the Patent Office contends that the administration of ACE inhibitors to control diabetes in rats would have inherently performed the same function as required by the rejected claims because they administer the same compounds to the same subjects.

Applicant neither agrees nor acquiesces to the above analysis by the Patent Office. However, Claims 1, 3, 10, 12, and 37 have been canceled, effectively rendering the rejection of these claims under 35 U.S.C. § 102(b) as being anticipated by Brown et al. or Uehara et al. moot. Applicant therefore respectfully requests withdrawal of the rejections under § 102(b).

Claim Rejection - 35 U.S.C. § 103

Claims 1-17 and 38-39 stand rejected by the Patent Office under 35 U.S.C. 103(a) as being unpatentable over Brown et al. in view of Vaughan (*Am J. Cardiol*, 1997; 79(5A):12-16), hereinafter referred to as "Vaughan".

The Patent Office admits that neither Brown et al. nor Vaughan specifically teaches that ACE inhibitors would be useful for inhibition of cardiovascular disease in healthy patients, including healthy post-menopausal female subjects. However, the Patent Office contends that the ordinary artisan would have had a reasonable expectation that an ACE inhibitor would be effective as claimed in light of the combined teachings of Brown et al. and Vaughan. Specifically, the Patent Office contends that one of skill in the art would be motivated to administer an ACE inhibitor to a person having a PAI-1 polymorphism, wherein the polymorphism produces excess levels of PAI-1 even if the patient appears otherwise healthy, because PAI-1 is a primary cause of thrombosis, which can lead to cardiovascular diseases, as taught by Vaughan.

The positions of the Patent Office as summarized above with respect to claims 1-17 and 38-39 are respectfully traversed as described below.

Initially, applicant notes Claims 1-17 and 39 have been canceled, effectively rendering the rejection of these claims under 35 U.S.C. § 103(a) as being obvious over Brown et al. in view of Vaughan moot. Applicant therefore respectfully requests withdrawal of the rejection of Claims 1-17 and 39 under § 103(a).

Regarding Claim 38, applicant respectfully submits neither Brown et al. nor Vaughan, either alone or in combination, teach or suggest each and every element of this claim. Claim 38 provides a method for significantly reducing a risk of cardiovascular disease in a post-menopausal female human subject by administering an effective dose of an ACE inhibitor to the post-menopausal female human subject.

None of the cited art teaches or suggests reducing a risk of cardiovascular disease in a post-menopausal female human subject. Brown et al. uses young male subjects stimulated to produce a state of induced activation of the renin-angiotensin system. Vaughan only proposes ACE inhibitor therapy as having benefit in patients with cardiovascular disease.

The Patent Office further suggests the ordinary artisan would have been motivated to treat a post-menopausal woman with an ACE inhibitor in order to reduce a risk of cardiovascular disease because the woman might be expected to exhibit increased PAI-1 levels and these increased levels of PAI-1 have been associated with cardiology related diseases. However, not all studies available to the skilled artisan at the time of filing of the present application corroborated this suggestion. For example, a journal publication by Lottermoser et al. (*Eur J Med Res*, 1999; 4(1):31-35; Applicant IDS dated July 19, 2002, reference no. 22) describes a study of the effects of captopril, an ACE inhibitor, in healthy humans. In this study, administration of captopril for two weeks showed no significant effect on PAI-1 levels. This study illustrates the ambiguity of the prophylactic effectiveness of ACE inhibitor administration for reduced risk of cardiovascular disease, particularly in post-menopausal female subjects. Thus, based on the teachings of *Lottermoser et al.*, a skilled artisan in the field could infer that ACE inhibition has no effect in reducing PAI-1 levels in healthy subjects.

Furthermore, as set forth in the specification at page 10, lines 4-15, although numerous therapeutic uses of ACE inhibitors were known at the time of filing the

present application, potential prophylactic uses for ACE inhibitors remained inconclusive. In particular, at the time of filing the present application, there was no FDA approved indication or other disclosure in the art of ACE inhibition as an agent for reducing PAI-1 levels, and thereby reducing risk of cardiovascular disease in a healthy population, including post-menopausal female human subjects, as recited in Claim 38.

Based on the conflicting teaching in the art prior to the presently disclosed subject matter, applicant respectfully submits that a skilled artisan would not be motivated to treat post-menopausal women with ACE inhibitors in order to reduce the risk of cardiovascular disease due to the overall ambiguity in the art as to the efficacy of such a practice. Therefore, applicant respectfully submits that none of the cited art teaches or suggests, either alone or in combination, each and every element of new claim 38.

Assuming *arguendo* the Patent Office has established a *prima facie* case of obviousness regarding claim 38, applicant respectfully submits unexpected results disclosed in the specification establish that the subject matter of claim 38 is patentable over the cited combination. *See, e.g., In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986); *In re May*, 574 F.2d 1082, 1094-95, 197 U.S.P.Q. 601, 611 (C.C.P.A. 1978); *In re Orfeo*, 440 F.2d 439, 442, 169 U.S.P.Q. 487, 489 (C.C.P.A. 1971); and *Ex parte Ebata*, 19 U.S.P.Q.2d 1952, 1956 (Bd. Pat. App. & Int. 1991).

Example 1 of the specification teaches the treatment of a group of healthy, normotensive post-menopausal women with either estrogen, ramipril (an ACE inhibitor) or a combination of estrogen and ramipril for a period of four weeks in order to determine the effects of these drugs on the lowering of PAI-1 levels in the test subjects, thereby reducing their risk for cardiovascular disease. Example 1 reported that although estrogen produced an expected decrease in PAI-1 levels, "[s]urprisingly, ACE inhibition also effectively lowered PAI-1 production in healthy normotensive, post-menopausal subjects (Table 1)." Specification at page 22, lines 14-16. As shown in Table 1 at page 23 of the specification, subjects treated with the ACE inhibitor exhibited a statistically significant 38% decrease in plasma PAI-1 levels. Even more unexpectedly, subjects treated with a combination of estrogen and ACE inhibitor exhibited decrease in plasma levels of PAI-1 53%, which is a greater decrease in PAI-1 levels than treatment with either drug alone, indicating a synergistic effect by the combination therapy. Finally, in all subjects, no change in tPA levels was observed, which indicates treatment with an ACE inhibitor improves the molar ratio of PAI-1/tPA in the blood, providing further protection against cardiovascular disease.

The study set forth in Example 1 clearly demonstrates treatment of normotensive post-menopausal women with an ACE inhibitor either alone, or in combination with estrogen unexpectedly provides protection against cardiovascular disease by lowering PAI-1 levels in the blood of the subjects. These unexpected results provide clear evidence of the non-obviousness of a method for significantly

reducing a risk of cardiovascular disease in a post-menopausal female human subject by administering an effective dose of an ACE inhibitor to the post-menopausal female human subject, as recited in Claim 38.

In summary, applicant respectfully submits neither Brown et al. nor Vaughan, either alone or in combination, teach or suggest each and every element of this Claim 38. Further, assuming the combined references did teach or suggest every element of Claim 38, applicant respectfully submits the ambiguity in the prior art teachings at the time of filing the present application with regard to the effectiveness of prophylactically treating a post-menopausal female with an ACE inhibitor in order to reduce risk of developing cardiovascular disease illustrates one of skill in the art would not be motivated to combine the references as suggested by the Patent Office. Finally, assuming *arguendo* the Patent Office has established Claim 38 is *prima facie* obvious in light of the combined references, applicant respectfully submits Claim 38 is patentably distinguished over the cited combination in light of the unexpected results discussed above and set forth in Example 1 of the specification. Therefore, applicant respectfully requests withdrawal of the rejection of Claim 38 as obvious over Brown et al. in view of Vaughan, and further respectfully requests allowance of Claim 38.

New Claims

New Claims 40-45 have been added by the present amendment as indicated above. No new matter is considered to have been added.

Claims 40-45 are essentially claims 2, 3, 7, 8, 9, and 6, respectively, rewritten to depend from claim 38, which recites a method for significantly reducing a risk of cardiovascular disease in a post-menopausal female human subject.

Claims 40-45 depend from Claim 38. Since the cited art does not teach or suggest all the elements of Claim 38, for the reasons stated above, the cited art does not teach or suggest all the elements of Claims 40-45 either. Accordingly, it is respectfully submitted that new claims 40-45 are patentably distinguished over the cited art. Allowance of these claims is therefore also respectfully requested.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

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DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

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